REMARKS

Claims 14, 31, 33-34 are withdrawn. Claims 11-12, 15, 35, 47-48, 50, 52-54 are cancelled. Claims 1, 10, 19, 21, 31, 46, 51 and 55 are amended. Claims 56-61 are added. Claims 1-10, 13-14, 16-34, 36-46, 49, 51, 55-61 are now pending. Reconsideration is respectfully requested in view of the following remarks.

I. Claim Objections

Claims 1, 11, 19, 30, 51, and 52 were objected to on the basis that they recite species that were not specifically elected.

A restriction requirement was made by a previous Examiner on July 5, 2001, requesting Applicants to elect between two species. The first specie (group I) covered a cell membrane impermeable reagent wherein the second domain of the reagent is a labeling domain. The second specie (group II) covered a cell membrane impermeable reagent wherein the second domain of the reagent is a binding domain.

During the telephone interview with the Examiner, it was agreed that the labeling domain and detecting domains are not independent and distinct species of invention and that the restriction requirement should be withdrawn. Therefore, Applicants respectfully request that the above claim objections be withdrawn.

II. Claim Rejections Under 35 U.S.C. 112, First Paragraph:

The Examiner rejected claims 52-54 under 35 U.S.C. 112, First Paragraph. As a result of Applicants' cancellation of claims 52-54, the above rejection is moot. Applicants respectfully request that the Examiner withdraw the above rejection.

III. Claim Rejections Under 35 U.S.C. 102(b):

The Examiner rejected claims 52-53 under 35 U.S.C. 102(b). As a result of Applicants' cancellation of claims 52 and 53, the above rejection is moot. Applicants respectfully request that the Examiner withdraw the above rejection.

IV. Claim Rejections Under 35 U.S.C. 103(a):

The Examiner rejected claims 1-11, 13, 16-30, 32, 36-51 and 55 under 35 U.S.C. 103(a) as being unpatentable over De La Fuente *et al.*, Hastie *et al.*, Rothschild *et al.* and Pierce Catalog

& Handbook, 1994-1995. In particular, the Examiner stated that the above references render the claimed invention obvious by providing a reasonable expectation of success. Applicants respectfully traverse the Examiner's rejection under 35 U.S.C. 103(a) for the following reasons.

Independent claims 1 and 19 as amended are directed to a method of labeling and a method of isolating a lumen-exposed molecule, respectively. Specifically, the claimed methods include a step of administering a cell membrane impermeable reagent having a cleavable chemical moiety that "is not cleavable under *in vivo* conditions but is cleavable under a condition that does not denature the lumen exposed molecules." Support for the amended language appears in the specification, for example, on page 8, lines 3-4 stating that "[i]n one embodiment, the conditions for cleaving the cleavable chemical moiety do not denature the reacted and isolated molecule" and on page 5, lines 8-11, which provide that the cleavable chemical moiety can be cleaved under relatively mild conditions such as "non-denaturing conditions."

None of the references cited by the Examiner teaches or motivates the claimed invention. In particular, De La Fuente *et al.* and Hastie *et al.* disclose the use of sulfosuccinimidyl 6-biotinamido hexanoate (NHS-LC-Biotin) for the identification and isolation of lumen-exposed molecules but fail to teach or motivate the use of an impermeable cell-membrane reagent that is **cleavable**. Rothschild *et al.* provides allegedly a general description of heterobifunctional crosslinkers for use in detection and isolation of biomolecules but fails to teach or motivate the administration of reagents into a perfusible space. In addition, Pierce Catalog & Handbook teaches the use of cleavable NHS-SS-biotin for isolating proteins from a mixture of proteins but fails to teach or motivate the administration of any reagents into a perfusible space.

None of the above references teaches or suggests, independently or in combination with another reference, the claimed method employing a cell membrane impermeable reagent with the following three structural domains:

- First domain: a chemical moiety domain that can covalently and non-specifically bind to a molecule exposed on the luminal surface of a cell lining of a perfusible space;
- Second domain: a labeling domain or a binding domain; and
- Third domain: a cleavable chemical moiety that is not cleavable under *in vivo* conditions but is **cleavable** under **a condition that will not denature the lumen-exposed molecule**, and/or optionally under **a condition that will not dissociate a complex** formed between the binding domain (e.g., biotin) and its ligand (e.g., avidin).

Independent claims 1, 19, and 51 utilize the above reagent and, therefore, are not obvious in light of the above references.

Furthermore, none of the above references teaches or suggests a method of labeling a molecule exposed on a luminal surface of a perfusible space *in situ* or *in vivo*, by administering to a perfusible space sulfosuccinimidyl-2-(biotinamido)ethyl-1,3-dithioproprionate as is described in claim 55. Therefore, claim 55 is not obvious in light of the above references either.

As none of the above references, independently or in combination, teaches or suggests the claimed invention, a prima facie case of obviousness has not been established. Therefore, Applicants respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In light of the remarks set forth above, Applicants believe that they are entitled to a letters patent. Applicants respectfully solicit the Examiner to expedite the prosecution of this patent application to issuance. Should the Examiner have any question, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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